The relation between the "treppe" in conductivity and fatigue is illustrated in the following measurements, taken in sequence from one experiment. The numbers not in brackets represent the intervals between stimuli in seconds; those bracketed are the consequent V-V intervals, the ventricle being used. 120.0 (0.42), 7.5 (0.54), 5.5 (0.59), 15.3 (0.68), 3.0 (0.39), 2.1 (0.44) 2.2 (0.51), 2.1 (0.64), 2.4 (blocked), 2.4 (0.70), 30.0 (blocked), 4.1 (0.42), 3.9 (0.52), 4.9 (blocked), 5.9 (blocked), 4.1 (0.57). It is evident that the "treppe" is most clearly marked after a rest of moderate duration (10 to 30 sec.). After a longer rest, the V-V interval is again short and the "treppe" does not appear, although the onset of fatigue is rapid. This seems to prove a difference between the condition of the tissue immediately responsible for the fatigue, and the condition favorable for the appearance of the supernormal phase. The experiment likewise proves that the supernormal recovery of conductivity may, like the recovery of excitability, be depressed by fatigue. Certain applications of these conclusions will be found in the following communication.

2877

Periods of spontaneous rhythm in the turtle heart and their bearing upon paroxysmal tachycardia.

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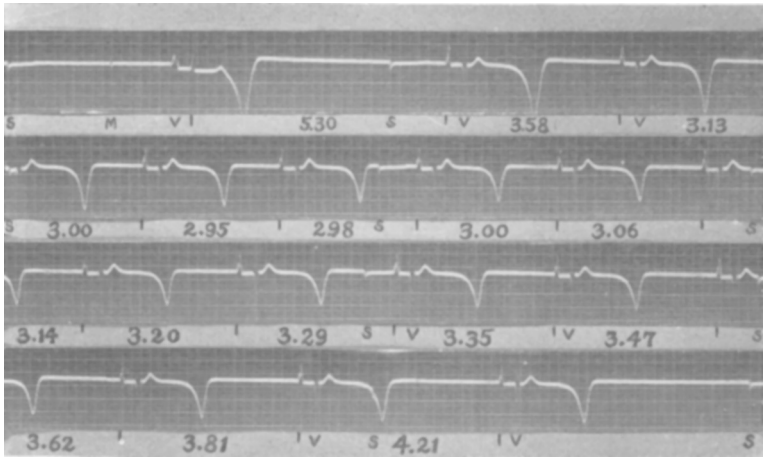
In frogs' hearts filled with mammalian serum and ligated between sinus venosus and auricles, or at other points, Luciani[1] observed and recorded periods of spontaneous rhythm separated by intervals of quiescence. We have obtained myograms and electrograms of the same phenomenon in turtle hearts perfused with strongly buffered, oxygenated physiological saline solutions at various H-ion concentrations. A typical period of auricular origin recorded with the string galvanometer is given in Figure 1. It will be noted that there is a rapid acceleration in the rhythm and then a more gradual retardation until the period ends.

[1] Luciani, *Human Physiology*, Eng. Trans., 1911, i, 302.

FIG. 1.



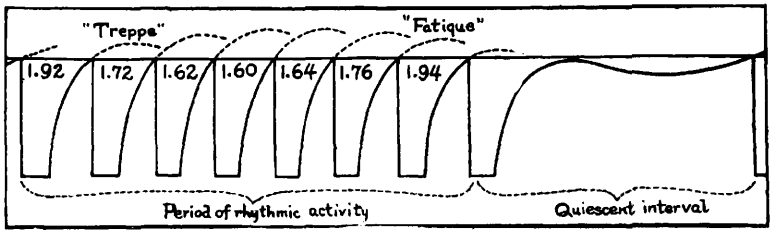
Electrogram of a complete period, initiated by a single break shock applied to the ventricle. S, the sinus negativity. The sinus was ligated off. M, the submininal make shock. V, beginning of ventricular response. The short vertical lines below the electrogram indicate the beginning of auricular negativity The numbers, the interauricular intervals.

Certain peculiarities in the time relations of the cycles during a period, and of the intervals between spontaneously initiated periods, suggested that their origin and course might readily be explained on the basis of a few well supported assumptions. *First,* that the impulses are discharged from an ectopic focus. Since the sinus is ligated off and since the time relations and electrograms seem to prove that the period is not due to circus contractions, there must be an ectopic focus. *Second,* that the impulse discharge depends upon the attainment of a sufficient degree of excitability in the focus. This is probable, for although highly excitable tissues are not necessarily spontaneously active, no one is likely to deny that the excitability is one determining factor where conditions are otherwise favorable to impulse discharge.[2] *Third,* that the returning excitability after each discharge passes through a supernormal phase. Adrian[3] has shown that nerve and muscle bathed in faintly acid solutions do show a supernormal recovery, *i. e.,* the excitability for a certain time

[2] Andrus, E. C., and Carter, E. P., *Heart,* 1924, xi, 97.
[3] Adrian, E. D., *J. Physiol.,* 1920, liv, 91.

after the response exceeds the resting (and depressed) excitability. *Fourth*, that there is a "treppe" in excitability for the first several recoveries of the period. It has been demonstrated that a "treppe" in *conductivity* may appear under suitable conditions in the compressed cardiac muscle of the turtle.[4] If, as is probable, conductivity is an aspect of excitability, we have here evidence for a "treppe" in excitability. *Fifth*, that the continued activity of the ectopic focus leads to its own fatigue. That the supernormal conductivity is depressed by fatigue is shown in a previous report in this number of the PROCEEDINGS. *Sixth*, that recovery from fatigue occurs during the quiescent interval between periods.

FIG. 2.



Schematic representation of the assumed changes in excitability in an auricular ectopic focus during and following a period of activity initiated in this case by a single induction shock applied to the ventricle. The numbers give the intervals between auricular beats. The heavy vertical lines represent the instants of impulse discharge. The short horizontal lines, the absolute refractory periods of the focus. The curves, the course of recovery of excitability in the focus. The continuous horizontal line, the threshold for impulse discharge. The dotted portions of the curves, the assumed course of recovery had the threshold been high enough to prevent impulse discharge. For convenience of representation, the quiescent interval is considerably shortened.

Figure 2 shows the postulated course of excitability during a period of activity and during a quiescent interval. With the above six points in mind, a study of this figure will make clear the mechanism which we suppose underlies the periodic rhythm in the turtle hearts in our experiments. Unless a supernormal phase and fatigue are factors involved it appears impossible to account for the sudden onset and end of the periods. In the absence of a supernormal the heart would presumably beat slowly and regularly.

[4] Ashman, R., *Am. J. Physiol.*, 1925, lxxiv, 140.

We have as yet found no definite relation between the periodicity and the pH of the perfusate. In view of Adrian's work, this is admittedly a difficulty. But there is no guarantee that the pH of the perfusate impresses itself upon all parts of the myocardium. Further, in each experiment, one auricle was not freely perfused and usually the periods were of auricular origin. However, in one or two instances the periods were of ventricular or junctional origin while the pH was 7.6.

Since the periods appeared in all our hearts which were perfused and rendered quiescent by ligation, it is to be anticipated that more than one ectopic focus might arise in the same heart. We have one excellent example of this sort, one focus being auricular, the other ventricular. Here the slower auricular focus was quickest to recover from fatigue and started the period. After it had discharged two or three impulses the more rapid ventricular focus, reaching its threshold by means of a "treppe", took over the rôle of pacemaker, but was soon fatigued. Then the auricular focus, not yet fatigued, was again able to initiate impulses and continued the period, with slower rhythm, to its conclusion.

Most interesting, because of its possible bearing on the problems of paroxysmal tachycardia and of ectopic beats in the human heart, was the effect of slow, rhythmic, electrical stimulation during the intervals between the periods of spontaneous rhythm. In general, if the rate of such stimulation was very slow the next spontaneous paroxysm was caused to appear earlier, but it was of shorter duration and of slower rhythm than the paroxysm appearing after complete rest. When the stimulation was somewhat faster, the time of appearance of the period was at the expected moment or somewhat delayed, the initial acceleration was less marked, and the duration was still further curtailed. Still more frequent electrical stimulation caused the period to appear still later and it was often limited to a *single ectopic beat.* Stimulation rapid enough to prevent recovery from fatigue completely suppressed the spontaneous activity.

It is thus clear that if an ectopic focus in the human heart possessed properties similar to those of the focus in the turtle hearts, it might, as permitted by conditions of nerve influence, sinus rhythm, and degree of supernormal recovery, discharge either single ectopic impulses, multiple ectopic impulses, or series of impulses producing paroxysms of tachycardia. It is to be

stressed that the ectopic focus is not in such cases to be regarded as a blocked-off focus, continuously rhythmically active at its own inherent rate,[5] but as a potential pacemaker, normally responding to every sinus impulse until conditions favor its assumption of the rôle of actual pacemaker. And it is further to be emphasized that a *very gradual* change in the condition of the focus could lead to the sudden onset or end of a paroxysm. We do not suppose, however, that all ectopic beats or all paroxysms of tachycardia are to be thus explained.

[5] Kaufmann, R., and Rothberger, C. J., *Zeitsch, f. d. ges. exper. Med.*, 1920, xi, 40.